Is the worldwide burden of asthma symptoms in school children changing? Global Asthma Network Phase I: repeated cross-sectional studies

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Abstract

Background

Asthma is the commonest chronic disease in children globally. The Global Asthma Network (GAN) Phase I aimed to determine if the worldwide burden of asthma symptoms is changing using the same methodology as the International Study of Asthma and Allergies in Childhood (ISAAC) Phase III

Methods

Asthma symptoms were assessed from centres which completed GAN Phase I and ISAAC Phase I (1993-5) and/or III (2001-3). The ten-yearly rate of change in prevalence was estimated for each centre and trends across world regions and income levels were estimated using mixed-effects linear regression models.

Findings

There were 119,795 participants from 27 centres in 14 countries: 74,361 13-14 year olds (adolescents) and 45,434 6-7 year olds (children) (response rates 90% and 79% respectively). About one in ten of both age groups had wheeze in the past year, of whom almost half had severe symptoms, and most centres showed a change in prevalence of ≥2 standard error ISAAC Phase III to GAN Phase I. Over the 27-year period adolescents showed a significant decrease in percentage point prevalence per decade in severe asthma symptoms (-0·37, 95% CI [-0·69, -0·04]) and an increase in asthma ever (1·25, 95% CI [0·67, 1·83]) and night cough (4·25, 95% CI [3·06, 5·44]), which was also found in children (3·21, 95% CI [1·80, 4·62]). The prevalence of current wheeze decreased in low-income countries (6-7 year-olds: -1·37, 95% CI [-2·47,-0·27], 13-14 year-olds: -1·67, 95% CI [-2·70,-0·64]), increased in lower-middle-income countries (6-7 year-olds: 1·99, 95% CI [0·33, 3·66], 13-14 year-olds: 1·69, 95% CI [0·13, 3·25]) but was stable in upper-middle and higher income countries.

Interpretation

Trends in prevalence and severity over the last three decades vary by age group, country income, region and centre. The high worldwide burden of severe asthma symptoms would be mitigated by enabling access to effective therapies for asthma.

Funding

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Research in context

Evidence before this study A recent review of worldwide trends in asthma prevalence found that the International Study of Asthma and Allergies in Childhood (ISAAC) has been the only global study providing direct evidence on changes in prevalence of asthma in school children.

Added value of this study The Global Asthma Network (GAN) Phase I adopting the identical ISAAC methods has produced the first comparable estimates of prevalence and severity of asthma symptoms in school children over nearly three decades; the worldwide populations were from 27 centres in 14 countries.

Implications of all the available evidence: Asthma is a major worldwide public health problem in school children. Implementing strategies to reduce prevalence and severity of asthma symptoms (and associated avoidable asthma morbidity and mortality and subsequent burden of related diseases including chronic obstructive pulmonary disease) should be a priority for the twenty-first century.

Introduction

Asthma is the commonest non-communicable disease in children and one of the commonest chronic diseases in adulthood.[1,2] It is a major global health problem with estimated 495,100 deaths from asthma in 2017,[3] and 22.8 million disability adjusted life years in 2017.[4] More than 1000 asthma deaths each day are comparable to the number deaths from malaria.[5] Cross-sectional comparisons of the prevalence of asthma in populations require standardised methods able to be implemented in a wide range of settings and the International Study of Asthma and Allergies in Childhood (ISAAC) is the only worldwide study to achieve this.[6] ISAAC Phase I (1993-5), repeated in Phase III (2001-3) identified that the prevalence of asthma symptoms (current wheeze) in school age children was rising in some low- and middle-income countries .[7,8]

The Global Asthma Network (GAN) was established in 2012 building on the success of ISAAC and incorporating a new collaboration with the International Union Against Tuberculosis and Lung Disease (The Union). One of GAN's core activities, GAN Phase I, building on ISAAC and using the identical approach and methods,[9] includes global surveillance of prevalence and severity of asthma symptoms,[10] making it the only source of new population-based data on worldwide trends in prevalence of asthma symptoms directly comparable to data from ISAAC Phases I and III. Public health interventions need to be based on science with up to date evidence of the size and trends of health issues.

The hypothesis relevant to the current manuscript was that globally, the burden (prevalence and severity) of asthma symptoms is changing in schoolchildren worldwide. The aim was to conduct asthma symptom surveillance around the world in two age groups of school pupils to examine time trends in prevalence and severity of asthma symptoms from centres which completed GAN Phase I and ISAAC Phase I and/or III.[10]

Methods

ISAAC Phases I and III were multi-centre, multi-country cross-sectional population studies in school children which followed standardised methodology which has been well described,[11,12] and is highly replicable.[13] This enabled comparisons of prevalence and severity of asthma symptoms between ISAAC Phases I and III and now GAN Phase I. Centres who completed GAN Phase I and ISAAC Phase I and/or III were the study centres for this analysis and key personnel at the GAN Global Centre, Auckland, New Zealand were the same throughout.

Each GAN Phase I investigator completed a registration document and followed the manual.[14] They gained approval from their local ethics committee and replicated identically the methodology used in their centres in ISAAC; this was documented in the Centre Report[14] which enabled checks to ensure the use of the same (as ISAAC) geographical sampling frame, sample size, age groups, method of selecting pupils, time of year for data collection, and the same translations.[15] From the sampling frame ≥10 schools were selected at random (or all schools if <10). The GAN Global Centre checked each Centre Report with the investigator for validity. Three centre datasets received (one for adolescents and two for children) were excluded from the analyses due to poor (<50%) response rates.

As in ISAAC the compulsory age group was 13-14 year olds (adolescents), who self-completed written questionnaires at school. The inclusion of 6-7 year olds (children) was optional and their questionnaires were completed at home by their parents. All students of the specified age within schools were included, selected by grade/level/year or by chronological age. Additionally GAN Phase I included questionnaires completed by the parents about themselves, not reported here. The sample size of 3000 that was sought in each age group (with a minimum of 1000 deemed acceptable) was stringent because of the number of hypotheses being tested.

The core written asthma questions used for comparisons in this paper were: “current wheeze” for a positive answer to the question: *“*Have you (has this child) had wheezing or whistling in the chest in the past 12 months?”. “Severe asthma symptoms” were defined as those with current wheeze who, in the past 12 months, had >4 attacks of wheeze, or >1 night per week sleep disturbance from wheeze, or wheeze affecting speech.[16] A positive answer to the question ‘‘Have you (Has this

child) ever had asthma?'' defined ''asthma ever''; "In the past 12 months, has your (has this child's) chest sounded wheezy during or after exercise?" defined "exercise wheeze"; "in the past 12 months have you (has this child) had a dry cough at night, apart from associated with a cold or chest infection?" defined "night cough".

The data and the Centre Report from each centre were submitted to the GAN Global Centre and quality control checks completed. Centres with minor deviations from the methodology were included in analyses, and these deviations specified in footnotes to the tables as in ISAAC.[17] The data were then transferred to one of two designated GAN Phase I data centres for checking and analysis: Murcia (Spain) for Spanish- and Portuguese-speaking centres, and London (United Kingdom) for all other languages. A uniform approach to data processing, checking and analysis was developed, using Stata versions 13–15.[18]

The mean date of questionnaire completion in each centre was used rather than just the year as occurred in ISAAC time trend studies.[7,8] High levels of participation were required for inclusion as absent school pupils may be away from school due to symptoms: response rate at least 80% for adolescents and 70% for children.[9,11,17] The response rate was defined as the number of core symptom questionnaires returned with at least some symptom data, divided by the number of pupils in the age group.

In each centre estimates of prevalence of symptoms for each age group were obtained by dividing the number of positive responses to each question by the number of completed questionnaires. If there were apparent inconsistencies between responses to the stem and branch questions these were accepted and not recoded. For regional and global summaries, the data for each centre was weighted by the sample size.

Country income category was obtained from the World Bank with countries categorised into low-, lower-middle-, upper-middle- and high-income countries.[19] The GNI 2001 classification was used as it was close to the timing of ISAAC Phase III where there is the most data. Countries were allocated to four regions corresponding to WHO regions of the world, with the South–East Asia and Western Pacific regions combined, and the Africa and Eastern Mediterranean combined, because of the

relatively small number of centres in each region. WHO regions and country income category are not synonymous.

We examined changes in prevalence over time from ISAAC Phase I to GAN Phase I. The 10-year change in prevalence of symptoms for each centre was calculated using the difference between the two time points (e.g. GAN Phase I and ISAAC Phase III) divided by the number of decades between the mean data collection dates of those time points.

We derived estimates of the absolute ten-yearly rate of change in current wheeze, severe asthma symptoms, asthma ever, exercise wheeze and night cough for each centre. The standard error (SE) of this change was calculated to take account of school level clustering.[18] Bland Altman plots were used to examine the relationship between change in prevalence and average prevalence between time points, to remove the influence of sampling error (regression to the mean)[20] when comparing the trends in higher or lower prevalence areas. The relationship was assessed using Spearman's rank correlation.

To examine trends over time in different types of countries or centres, multi-level modelling was undertaken. Along with GAN Phase I centres who undertook ISAAC we included ISAAC-only centres with data from both ISAAC Phases I and III[7] (94 centres with adolescents and 57 centres with children). This enabled us to estimate trends in prevalence across the full 27-year time period (1993-2020) using all available time trends centres in one mixed-effects linear regression model. Some centres had complete three-point time trend data available for ISAAC Phase I to ISAAC Phase III to GAN Phase I, others had only ISAAC Phase III to GAN Phase I, or ISAAC Phase I to GAN Phase I, or ISAAC Phase I to Phase III.

We included country- and centre-level random intercepts in the mixed-effects linear regression models. The estimated time trend can therefore be interpreted as the within-centre, absolute change in percentage point prevalence per decade. Data from both age groups were included in the one model to improve model efficiency. We included age group as an *a priori* confounder and effect modifier in order to assess time trends in each age group separately.

We considered country income category and region as confounders and effect modifiers of the time trend. Thus our analyses controlled, by stratification, for age group, region of the world and income level of country. In all centres boys and girls were about 50%, so sex was not controlled for. We also tested for evidence against a linear form for the time trend through the introduction of a quadratic term. The main models were additionally fitted to estimate the time trend in severe wheeze, exercise wheeze, night cough and asthma ever.

To consider the effect of level of prevalence of current wheeze on the change in prevalence, we additionally fitted separate models which included level of prevalence in ISAAC Phase III (or mid-point if no ISAAC Phase III data available).

Role of the funding source

The funding sources had no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Results

Data were available for 27 centres in 14 countries in all four regions, for which GAN Phase I methodology and data checks were completed by January 2021 and ISAAC Phase I and/or III had also been previously completed. Overall, 119,795 GAN Phase I participants were included: 74,361 adolescents in 27 centres (response rate 90%, range 67·5-100%) and 45,434 children in 19 centres (response rate 79%, range 55·2-100%) (Tables 1 & 2 and Web Tables 1& 2). For the 27 centres in GAN Phase I with data on adolescents, 13 had data from ISAAC Phase III only, 13 had data from both ISAAC Phases I and III, and one (Athens) had ISAAC Phase I data only. For the 19 centres in GAN Phase I with data on children, nine had data from ISAAC Phase III only, nine had data from both ISAAC Phases I and III, and one (Chandigarh) had ISAAC Phase I data only.

GAN Phase I was undertaken between March 2015 and February 2020, with the date of data collection varying by centre. Between ISAAC Phase III and GAN Phase I there was an average of 15·4 years (range 12·7 to 17·3) and between ISAAC

Phase I and GAN Phase I 22·7 years (range 19·5 to 25·5) for the adolescents dates of data collection in children were similar.

For current wheeze, in GAN Phase I the prevalence ranged in adolescents from 0·9% (New Delhi) to 21·3% (Cape Town), with a mean of 10·4% 95% CI [7·8, 12·8], and in children from 1·1% (Lucknow) to 23·2% (Costa Rica), with a mean of 9·9% 95% CI [7·3, 12·4]. The Bland Altman plots showed that the underlying prevalence of current wheeze was not associated with the magnitude of change (Web Figure 1).

Figure 1, shows the changes within centres in absolute prevalence of current wheeze from ISAAC (Phases I and III) to GAN Phase I. Within each age group, most centres in both age groups demonstrated significant (≥2 SE up or down) changes in current wheeze and similarly for severe asthma symptoms.In adolescents 9, 7 and 10 centres showed a ≥2 SE decreased, ≥2 SE increased or ≤2 SE change in the prevalence of current wheeze, respectively (Web Figure 2a), whilst in children 9, 5 and 4 centres showed a ≥2 SE decreased, ≥2 SE increased or ≤2 SE change (Web Figure 3a). Additionally, within centres, in both age groups, the pattern of changes in prevalence of severe asthma symptoms (Web Figures 2b and 3b) and asthma ever (Web Figures 2c and 3c) was similar to changes in current wheeze. Moreover, the pattern of changes in prevalence of exercise wheeze and night cough (Tables 1 & 2) was similar to those in current wheeze in both age groups.

The regression models examined whether within-centre changes were, collectively, compatible with chance, or real trends. They showed the effects of age group, region and country income group upon time trends in current wheeze to be minimally altered by adjustment for their mutual confounding (data not shown). Although there was no evidence for age group as an effect modifier (p = 0·67) we decided *a priori* to stratify on this variable, due to the importance of showing age group-specific results. There was evidence of additional effect modification with both income group (p=0·002) and region (p=0·0002) but the low number of centres in each stratum meant that we did not consider these effect modifiers together.

After stratifying by age group, adolescents showed a decrease in percentage point prevalence per decade in severe asthma symptoms (-0·37, 95% CI [-0·69, -0·04], and an increase in asthma ever (1·25, 95% CI [0·67, 1·83]) and in night cough (4·25,

95% CI [3·06, 5·44]), which was also found in children (3·21, 95% CI [1·80, 4·62]) (Table 3). Stratification by country income group (adjusted for region) showed a decrease in prevalence of current wheeze among low-income countries (6-7 year-olds: -1·37, 95% CI [-2·47,-0·27], 13-14 year-olds: -1·67, 95% CI [-2·70,-0·64]). However, an increase in prevalence of current wheeze was found among lower-middle-income countries (6-7 year-olds: 1·99, 95% CI [0·33, 3·66], 13-14 year-olds: 1·69, 95% CI [0·13, 3·25]), but no change in upper-middle- and high-income countries. Stratification by world region (adjusted for income group) showed an increase in prevalence of current wheeze in the Africa and Eastern Mediterranean region for both age groups (6-7 year-olds: 2·61, 95% CI [0·76, 4·46], 13-14 year-olds: 2·09, 95% CI [0·40, 3·78]). South-East Asia and Western Pacific regions showed decreased prevalence of current wheeze in both age groups (6-7 year-olds: -1·35, 95% CI [-2·28,-0·41], 13-14 year-olds: -1·87, 95% CI [-2·78,-0·96]). There was no evidence of a change in prevalence for the regions of America and Europe in either age group. There were 18 strata and five symptom outcomes but those for different symptoms are not statistically independent.

The results of the models for the four other outcome variables showed the pattern for severe asthma symptoms and exercise wheeze was similar to the pattern of current wheeze (Table 3). However, asthma ever showed a different pattern with increases in high-income countries and Europe. For night cough there was a consistent pattern of increase in point prevalence in both age groups, all country income groups and most regions.

Discussion

GAN Phase I has provided the first global estimates of trends over time in prevalence and severity of asthma symptoms since 2003. It included almost 120,000 children from 27 centres in 14 countries using the same instruments and methodology as ISAAC[9,10]. We identified a substantial burden of asthma symptoms in school children: in both age groups, about one in ten had wheeze in the past year, of whom almost half had severe symptoms. We modelled all ISAAC Phases I and III and GAN Phase I prevalence data over time to determine patterns of change over nearly three decades (1993-2020) and found prevalence and severity to vary by age group, country income, region and centre.

Change in prevalence of all asthma symptoms by ≥2 SE was seen in most centres suggesting more than just random variation. In seven countries there was a decrease in prevalence of most asthma symptoms, and in seven increases were found. There is evidence from the 27-year modelling of an overall decrease in prevalence for severe asthma symptoms in adolescents and an overall increased report of asthma ever and night cough in both age groups. We also found regional differences with evidence of increasing prevalence of current wheeze and severe asthma symptoms in Africa and Eastern Mediterranean and decreasing in South-East Asia and Western Pacific regions; country income was associated with changes in prevalence of asthma symptoms with low-income countries showing a significant decrease but lower-middle-income countries showing an increase, with no evidence of change in more affluent countries. These broad patterns overlie substantial heterogeneity of trends both between and within countries. This limits the generalisability of conclusions from any single centre or country.

The interpretation of these patterns is complex, as there are a wide range of risk factors, and environmental changes at play. Some centres had changes of particular interest. Large variations were found within India, and the reasons for this are subject to a national study. A few high prevalence centres progressively decreased from ISAAC Phases I to III[7,8] to GAN Phase I. Some low prevalence centres showed increased prevalence of asthma symptoms including severe asthma symptoms contributing to the burden of asthma. A large increase in prevalence was found in Lattakia in war-torn Syria. In two centres (Cape Town, Bilbao) the increase in prevalence of severe asthma symptoms was more than that of asthma symptoms; whether this is due to barriers to asthma care remains to be investigated. The influence of asthma programmes, accessibility of asthma medicines, or other environmental changes[1] on these variations needs to be determined. National asthma programmes can be effective ways of reducing the burden of severe asthma symptoms: Costa Rica, India, and Taiwan reported national asthma strategies in 2013-14,[21] which may be a factor in the decreased burden in the first two of these countries, but not in Taiwan. The role of macro-environmental changes affecting populations are worthy of exploration.

The Global Burden of Disease Study (GBD) has reported estimates of global asthma prevalence (all ages) over a similar time period as this analysis. The GBD case definition for asthma differed from ours in that it was reported diagnosis by a physician (which varies between countries) combined with wheezing in the past 12 months. The GBD estimates over 2000-2017 showed large and unexplained variations between 220·4-339·4 million[2,22-27] Since 2003 there have been no new worldwide standardised studies of asthma symptom prevalence until GAN Phase I which includes non-time trends centres and should contribute to future GBD analyses.

There are many strengths of this study, especially the standardised methodologies used to estimate asthma prevalence from symptoms in a wide range of settings in the world.[6] Tight quality control checks along with the same key personnel in ISAAC and GAN meant that replication of the standardised methodology from ISAAC Phase I to III to GAN Phase I was successful, as evidenced by the low number of centres excluded or with footnotes on methodology. Response rates were high. The study includes a large number of centres from low-, middle- and high-income countries from all regions of the world except North America. In about half of the centres GAN Phase I was the first paired standardised study of asthma symptom prevalence; these included centres in five countries with no previous time trend data (centres in Ecuador, Greece, Nicaragua, Sudan and Syrian Arab Republic), and nine centres which had no previous time trend data (although different centres in those countries had provided ISAAC time trends data)[8].

There are limitations with the study which include the smaller number of GAN Phase I centres compared with ISAAC Phase I to III, which makes it difficult to generalise the findings to global prevalence changes. Centres were self-selecting and therefore not representative of countries except for Costa Rica which was a whole country study. Within an individual country there may be wide differences of prevalence such as rural vs urban locations and high-income areas in a low- or middle-income country. Despite the simplicity of the GAN/ISAAC approach, it is more difficult to undertake these surveys now than at the time of ISAAC Phases I and III. Factors include reluctance of schools to being involved in research due to increased curriculum demands; more stringent ethics requirements meaning it is less easy to

obtain passive consent for adolescents,[28] funders not prioritising population-based research; parents being busier and having less time for participation; pandemics (currently COVID-19) and conflicts which disrupt schools and people's lives.

Future GAN Phase I reports will contribute an estimate of the global burden of asthma which will include the GAN Phase I centres in this paper as well as those with centres without time-trend data, and analyses on rhinoconjunctivitis and eczema and other asthma risk factors, similar to ISAAC Phase III reports, as well as studies in adults. Extensive risk factor analyses were undertaken in ISAAC Phase III.[29,30] Equivalent analyses will be undertaken using GAN Phase I data in conjunction with ISAAC Phase III data to determine to what extent changes in risk factor prevalences over time can account for the observed changes in prevalence and severity of asthma symptoms. We will also examine the relationship of management of asthma and symptoms. There is abundant evidence that in many locations in the world asthma management is suboptimal contributing to a relatively high prevalence of severe asthma symptoms[1,3] and there are strategies to improve this even in localities within low-resource settings.[1, 31] As the legacy of severe asthma in childhood can be chronic obstructive pulmonary disease in adults, reducing the burden of severe asthma symptoms in children is of vital importance.[2]

These data suggest that while the overall worldwide prevalence of asthma symptoms is relatively stable, about 1 in 20 school children have severe asthma symptoms, and they need to gain better asthma control to lessen associated avoidable asthma morbidity and mortality; little has changed over 27 years. The United Nation's 2030 Sustainable Development Goal 3 aims to "ensure healthy lives and promote well-being at all ages".[1] Our findings emphasise the urgency of ensuring that the high worldwide burden of severe asthma symptoms in children is mitigated by enabling equitable and affordable access to the effective therapies for asthma that have been available to those who can afford them for decades.

Declaration of interests

The authors declare that they have no conflict of interest.

ILLUSTRATIONS

Legends for Figures

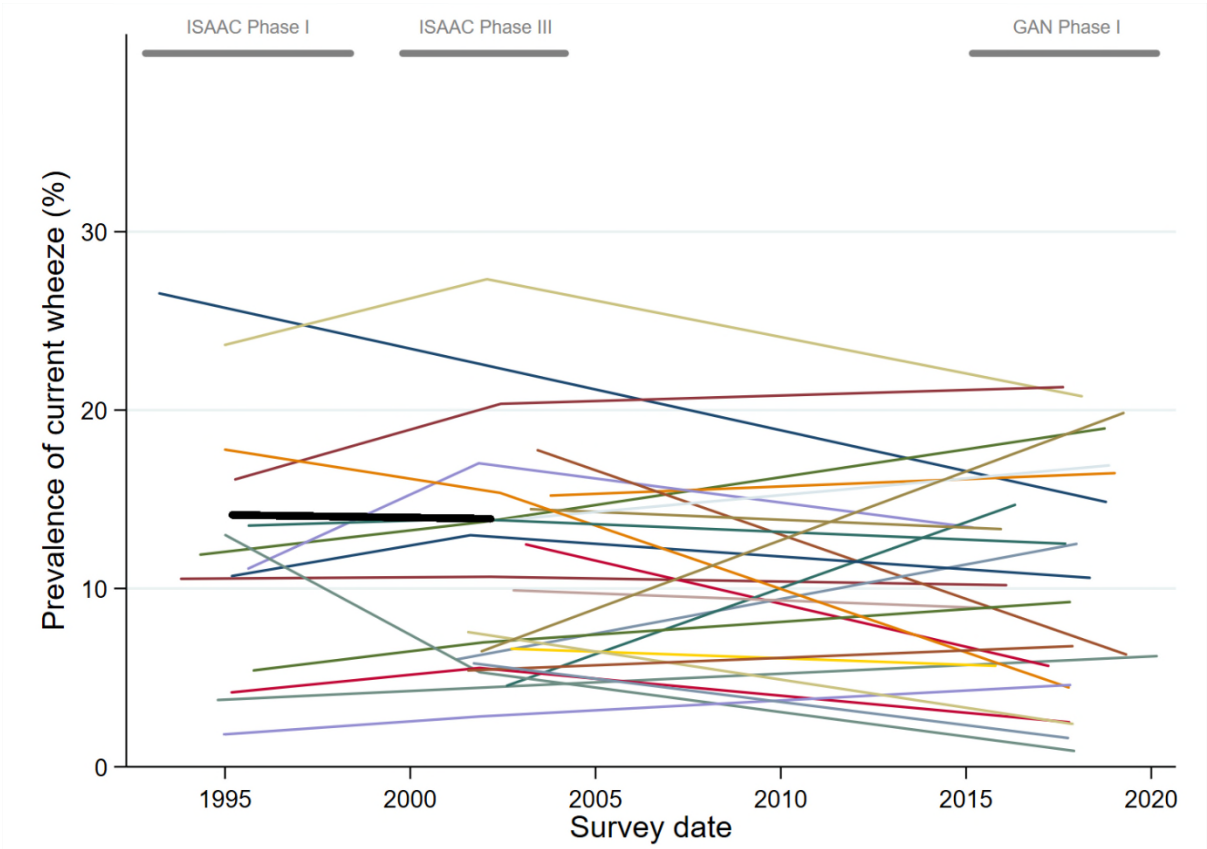
Figure 1a

Absolute changes over time in prevalence of current wheeze for 13-14 year olds (adolescents) by mean survey date. Each coloured thin line represents one centre. The thick black line shows the average absolute change from ISAAC Phase I to Phase III for those centres which did not participate in GAN Phase I. The span of the years of data collection for ISAAC Phase I, ISAAC Phase III and GAN Phase I are shown.

Figure 1b

Absolute changes over time in prevalence of current wheeze for 6-7 year olds (children). Each coloured thin line represents one centre. The thick black line shows the average absolute change from ISAAC Phase I to Phase III for those centres which did not participate in GAN Phase I. The span of the years of data collection for ISAAC Phase I, ISAAC Phase III and GAN Phase I are shown.

Figures 1a (upper) and 1b (lower)



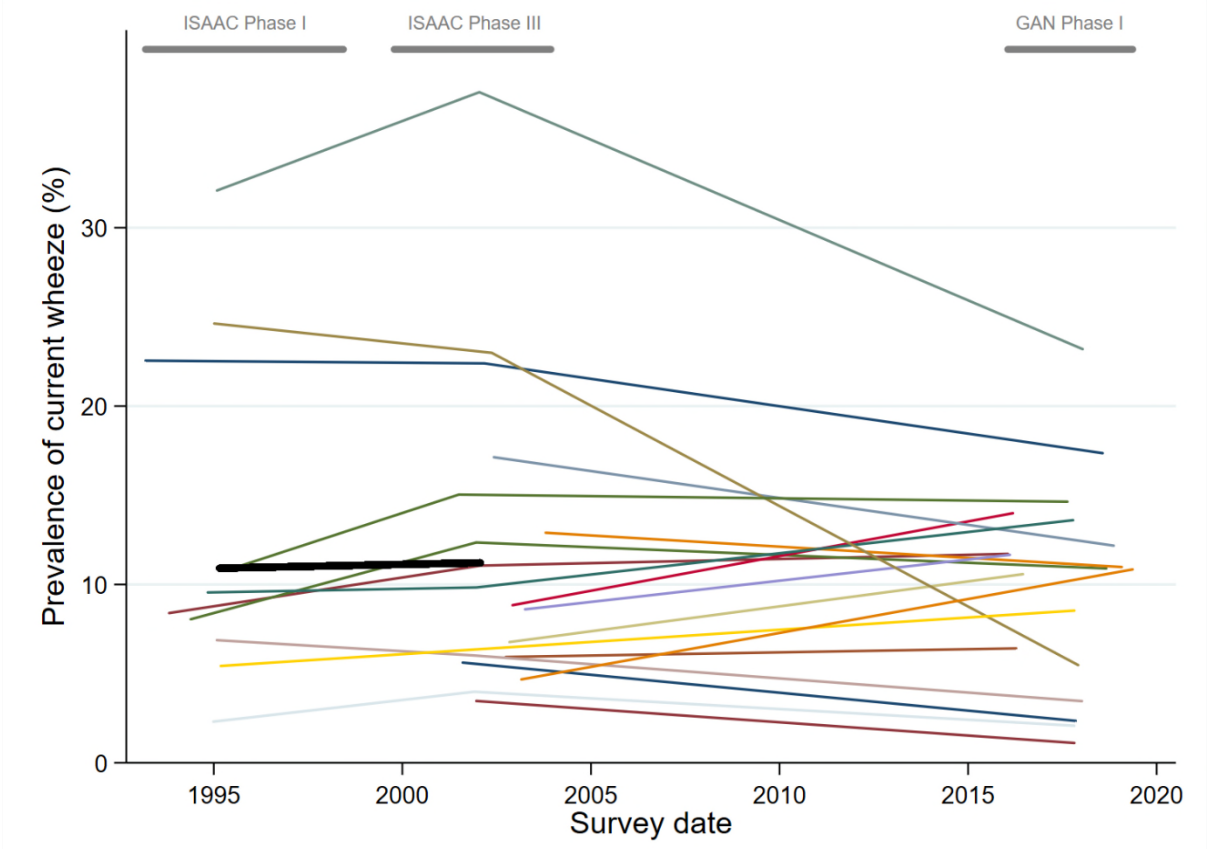


Table 1: 13-14 year age group participating centres, principal investigators, GAN Phase I and ISAAC Phase III, date of data collection, numbers of individuals, response rate, 12-month prevalence of asthma symptoms for each centre, by region, in all phases, average change per year and SE of the change.

				Mean data collection date	Years between phases	Number of individuals	Wheeze in past 12 months			Ever had asthma			Severe asthma symptoms in past 12 months			Exercise wheeze in past 12 months			Night cough in past 12 months		
							Prevalence	Absolute change per decade	Number of SEs change	Prevalence	Absolute change per decade	Number of SEs change	Prevalence	Absolute change per decade	Number of SEs change	Prevalence	Absolute change per decade	Number of SEs change	Prevalence	Absolute change per decade	Number of SEs change
Country	Centre	PI	GAN* response rate	GAN	ISAAC III to GAN	GAN	GAN	ISAAC III to GAN	ISAAC III to GAN	GAN	ISAAC III to GAN	ISAAC III to GAN	GAN	ISAAC III to GAN	ISAAC III to GAN	GAN	ISAAC III to GAN	ISAAC III to GAN	GAN	ISAAC III to GAN	ISAAC III to GAN
Africa and Eastern Mediterranean							%	%		%	%		%	%		%	%		%	%	
Nigeria	Ibadan[1]	*A Falade*	85·0	May-18	16·7	2,897	10·6	-1·4	-1·0	3·7	-4·8	-5·3	6·2	-1·3	-1·2	32·0	-1·3	-0·7	23·6	-2·5	-1·8
South Africa	Cape Town	*HJ Zar*	84·4	Aug-17	15·2	3,979	21·3	0·6	0·5	16·6	1·4	1·5	12·0	1·7	2·7	36·0	2·2	1·3	41·4	3·1	2·4
Sudan	Khartoum	*M Nour*	99·9	Mar-17	14·1	1,785	5·7	-4·8	-3·9	18·2	1·9	1·2	3·5	-2·7	-3·2	28·1	9·6	3·4	40·4	14·4	7·2
Syrian Arab Republic	Lattakia	*G Dib*	99·6	Apr-19	17·3	1,215	19·8	7·7	4·4	10·9	2·8	4·9	10·6	4·7	4·3	35·8	13·6	4·6	54·4	19·4	8·6
Region total				Dec-17	15.7	9,876	15·1	0·7	na	12·4	0·1	na	8·6	0·8	na	33·4	5·4	na	37·6	6·2	na
America																					
Chile	South Santiago	*J Mallol*	81·9	Mar-15	13·3	2,750	13·4	-2·7	-3·2	13·7	-1·7	-2·4	3·9	-1·4	-3·2	16·7	-3·0	-3·5	32·9	-5·7	-5·6
Costa Rica	Costa Rica[2]	*M Soto-Martinez*	67·5	Feb-18	16·1	1,338	20·8	-4·1	-3·9	22·0	-0·7	-0·6	9·4	-2·7	-3·7	14·4	-3·3	-4·4	31·2	3·0	2·7
Ecuador	Quito[3]	*A Cabrera Aguilar*	100·0	Apr-19	15·9	3,000	6·3	-7·2	-6·5	4·5	-1·5	-2·5	3·0	-1·4	-2·5	18·2	4·8	3·3	28·0	12·7	9·4
México	Ciudad Victoria[4]	*R García-Almaráz*	82·3	Dec-15	12·7	2,468	13·3	-0·9	-0·4	8·6	2·2	2·6	5·8	0·4	0·7	16·6	-3·9	-1·5	25·8	-5·6	-2·0
México	Mexicali	*JV Mérida-Palacio*	83·7	Apr-16	13·7	2,479	14·7	7·4	11·5	8·7	5·4	11·6	7·5	3·9	8·4	21·3	11·2	7·3	25·7	16·4	11·7

México	México City (North Area)[4]	*BE Del Río Navarro*	93·8	Sep-15	12·9	3,375	8·9	-0·8	-0·6	7·4	-0·4	-0·4	3·7	-0·2	-0·3	15·5	1·9	1·3	14·8	-13·2	-4·7
México	Monterrey[5,6]	*SN González-Díaz*	88·0	Dec-17	16·7	2,641	12·5	3·9	6·9	11·3	2·5	4·2	5·5	1·7	4·0	23·1	8·0	7·6	31·2	-2·6	-1·1
México	Toluca Urban Area[4]	*EM Navarrete-Rodriguez*	98·1	Oct-15	13·1	2,650	5·7	-0·7	-0·7	6·2	0·8	1·8	2·3	-0·9	-1·3	11·0	-5·2	-1·6	16·1	-3·4	-1·2
Nicaragua	Managua	*JF Sánchez*	90·5	Nov-18	16·5	3,131	16·9	1·9	2·3	20·1	3·0	4·1	9·8	1·3	2·2	21·9	-2·6	-2·6	43·8	0·2	0·2
Region total				Dec-16	14.5	23,832	11·9	-0·5	na	10·8	0·9	na	5·4	0·0	na	17·8	1·2	na	27·5	0·2	na
Europe																					
Spain	A Coruña	*A López-Silvarrey Varela*	92·1	Jan-19	15·2	3,462	16·5	0·8	1·1	20·6	1·4	1·9	8·1	1·2	2·5	21·3	0·2	0·2	35·7	4·9	4·6
Spain	Bilbao	*C González Díaz*	91·1	Sep-18	16·8	3,379	19·0	3·1	4·8	29·9	4·8	6·4	9·6	2·2	5·9	26·9	2·8	3·0	35·3	8·9	8·6
Spain	Cartagena[2]	*L García-Marcos*	73·8	Jan-16	13·9	3,437	10·2	-0·3	-0·5	14·9	2·3	3·4	4·1	0·1	0·3	13·9	-0·8	-0·9	23·6	-2·8	-3·0
Region total				Dec-17	15.4	10,278	15·2	1·4	na	21·7	3·1	na	7·3	1·3	na	20·7	1·0	na	31·5	4·0	na
South-East Asia and Western Pacific																					
India	Bikaner	*M Sabir*	90·1	Nov-17	16·3	2,702	2·4	-3·2	-3·2	3·5	-0·7	-1·1	1·6	-0·9	-1·7	8·7	-0·1	-0·1	22·5	-2·5	-2·4
India	Chandigarh[7]	*M Singh*	100·0	Oct-17	15·9	3,000	2·5	-1·9	-5·6	1·2	-1·7	-5·0	0·7	-1·2	-5·8	10·4	3·2	2·2	39·1	7·8	3·8
India	Jaipur	*V Singh*	98·7	Nov-17	16·3	3,060	6·8	0·8	1·1	6·2	0·2	0·3	2·1	-0·5	-1·6	9·8	3·3	5·9	45·8	11·4	8·2
India	Kottayam[8]	*TU Sukumaran*	85·3	Oct-17	15·3	2,091	4·4	-7·1	-5·9	4·3	-3·0	-2·0	1·5	-5·0	-4·1	4·8	-4·5	-4·1	17·3	-7·6	-5·0
India	Lucknow	*S Awasthi*	94·0	Oct-17	16·0	2,969	1·6	-2·6	-4·6	1·3	-1·2	-2·6	0·8	-1·2	-3·1	9·5	2·0	1·5	22·7	-4·9	-1·5
India	New Delhi (7)	*SK Kabra*	100·0	Nov-17	16·0	3,024	0·9	-2·8	-4·2	0·3	-3·9	-5·2	0·5	-1·8	-4·7	6·6	1·2	1·7	27·3	13·1	12·6
India	Pune	*S Salvi*	99·6	Oct-17	15·9	3,030	4·6	1·1	2·2	7·9	1·7	2·3	2·0	1·2	5.1	10·6	2·6	2·7	33·0	14·2	9·0
New Zealand	Auckland[4]	*MI Asher*	85·5	Oct-18	16·7	1,885	14·9	-4·6	-3·4	22·6	-3·2	-3·0	5·1	-2·2	-3·6	22·7	-5·8	-5·2	24·9	-3·6	-2·6
Taiwan	Taipei[1]	*J-L Huang*	93·0	Oct-17	15·8	3,474	9·2	1·4	2·9	14·2	-1·7	-2·7	3·3	0·7	2·7	25·0	3·6	4·8	27·7	9·6	13·5
Thailand	Bangkok[4,9]	*S Chinratanapisit*	97·9	Sep-17	16·1	3,206	12·5	-0·9	-0·7	8·8	-4·4	-5·9	5·8	-0·4	-0·6	14·8	-2·0	-1·4	30·0	-0·7	-0·2
Region total				Nov-17	16.0	28,441	5·8	-2·1	na	6·7	-2·5	na	2·3	-1·2	na	12·4	-0·1	na	29·7	4·3	na
World total				Aug-17	15·4	72,427	10·4	-0·7	na	11·0	-0·3	na	4·9	-0·2	na	18·2	1·2	na	30·3	3·2	na

*GAN Phase I

Methodology notes for GAN Phase I centres only: 1 No date of birth on the questionnaire; 2 response rate <80%; 3 age and birth date show high inconsistencies; 4 <10 schools used if ≥10 schools available; 5 only reported age reliable; 6 Single data entry; 7 no age on questionnaire; 8 questionnaires completed at home by parents; 9 >20% missing age and date of birth.

Athens is not in this Table because it's ISAAC data is only from Phase I.

Table 2: 6-7 year age group participating centres, principal investigators, GAN Phase I and ISAAC Phase III, date of data collection, numbers of children, response rate, 12-month prevalence of asthma symptoms for each centre, by region, in all phases, average change per year and SE of the change.

				Mean data collection date	Years between phases	Number of individuals	Wheeze in past 12 months			Ever had asthma			Severe asthma symptoms in past 12 months			Exercise wheeze in past 12 months			Night cough in past 12 months		
							Prevalence	Absolute change per decade	Number of SEs change	Prevalence	Absolute change per decade	Number of SEs change	Prevalence	Absolute change per decade	Number of SEs change	Prevalence	Absolute change per decade	Number of SEs change	Prevalence	Absolute change per decade	Number of SEs change
Country	Centre	PI	GAN* response rate	GAN	ISAAC III to GAN	GAN	GAN	ISAAC III to GAN	ISAAC III to GAN	GAN	ISAAC III to GAN	ISAAC III to GAN	GAN	ISAAC III to GAN	ISAAC III to GAN	GAN	ISAAC III to GAN	ISAAC III to GAN	GAN	ISAAC III to GAN	ISAAC III to GAN
Africa and Eastern Mediterranean							%	%		%	%		%	%		%	%		%	%	
Syrian Arab Republic	Lattakia	*Y Mohammad*	93·0	May-19	16·2	1,116	10·8	3·8	5·1	11·9	4·9	5·2	5·4	1·7	3·2	11·6	5·5	6·7	29·1	8·6	4·4
Region total				May-19	16.2	1,116	10·8	3·8	na	11·9	4·9	na	5·4	1·7	na	11·6	5·5	na	29·1	8·6	na
America																					
Costa Rica	Costa Rica[1]	*M Soto-Martinez*	64·5	Jan-18	16·0	1,936	23·2	-9·0	-7·5	29·3	0·9	0·6	13·2	-3·2	-4·1	12·2	-3·0	-3·5	45·9	5·6	5·5
México	Ciudad Victoria	*R García-Almaráz*	81·5	Feb-16	12·9	2,444	11·7	2·4	3·9	6·5	1·4	2·5	5·8	1·8	4·4	10·0	4·5	7·1	22·7	-4·6	-4·3
México	Mexicali	JV Mérida-Palacio	77·0	Mar-16	13·3	2,001	14·0	3·9	5·7	7·5	-0·2	-0·4	7·6	3·3	5·9	14·8	7·0	10·3	23·0	-3·4	-2·8
México	México City (North Area)	*BE Del Río Navarro*	86·7	Jun-16	13·6	2,515	10·6	2·8	4·2	5·1	0·5	1·0	4·3	1·5	4·1	9·1	4·2	7·5	19·8	-7·9	-5·6
México	Toluca Urban Area	*EM Navarrete-Rodriguez*	95·7	Apr-16	13·5	2,712	6·4	0·4	0·4	3·4	1·0	2·6	2·9	0·7	1·4	6·5	2·2	3·2	18·0	-0·6	-0·5
Nicaragua	Managua	*JF Sánchez*	87·9	Nov-18	16·4	3,162	12·2	-3·0	-3·0	14·0	-1·8	-1·9	5·9	-2·1	-3·2	7·9	-4·9	-5·9	32·5	-7·2	-3·7
Region total				Jan-17	14.4	14,770	12·5	-1·5	na	10·4	-0·4	na	6·3	-0·3	na	9·7	0·8	na	26·5	-3·4	na
Europe																					
Spain	A Coruña	*A López-Silvarrey Varela*	71·0	Jan-19	15·3	3,407	11·0	-1·3	-2·3	9·7	-2·6	-4·5	4·4	-0·2	-0·4	4·9	-0·8	-2·0	30·9	4·8	5·1
Spain	Bilbao[1]	*C González Díaz*	55·2	Aug-18	16·7	2,707	10·9	-0·9	-1·4	22·7	1·2	1·4	4·1	0·2	0·4	6·4	-0·1	-0·3	27·8	4·2	5·0
Spain	Cartagena[1]	*L García-Marcos*	65·9	Jan-16	14·0	3,509	11·7	0·5	0·9	10·3	-0·3	-0·6	4·4	0·2	0·4	6·1	0·7	1·7	27·4	4·7	5·6
Region total				Nov-17	15.3	9,623	11·2	-0·6	na	13·6	-1·1	na	4·3	0·1	na	5·7	-0·1	na	28·7	4·6	na
South-East Asia and Western Pacific																					
India	Jaipur	V Singh	75·8	Nov-17	16·3	2,296	2·4	-2·0	-2·1	2·2	-2·2	-2·3	0·8	-1·7	-2·0	2·5	-0·6	-0·5	19·9	-2·9	-2·3
India	Kottayam[1]	*TU Sukumaran*	68·4	Dec-17	15·5	2,099	5·5	-11·3	-13·4	3·5	-5·2	-3·7	2·9	-5·3	-4·8	1·8	-7·1	-6·2	20·9	-0·3	-0·2
India	Lucknow	*S Awasthi*	91·3	Oct-17	15·9	2,969	1·1	-1·5	-3·3	0·6	-1·1	-3·7	0·5	-0·6	-2·7	1·9	0·2	0·6	6·7	-5·7	-5·0
India	New Delhi [7]	*SK Kabra*	80·9	Jan-18	16·1	2,516	3·5	-1·6	-2·6	0·4	-3·9	-5·7	0·8	-1·1	-5·8	2·7	-0·2	-0·6	22·9	9·8	7·8
India	Pune	S Salvi	79·8	Oct-17	15·9	2,404	2·1	-1·2	-3·4	1·8	-1·0	-3·6	0·7	0·4	4·1	4·4	0·8	1·7	19·8	5·0	5·3

New Zealand	Auckland[1]	*MI Asher*	63·7	Jul-18	16·4	1,538	17·4	-3·1	-3·6	19·2	-5·5	-4·5	6·7	-2·0	-3·4	12·0	-2·1	-2·3	24·8	-2·7	-2·7
Taiwan	Taipei[2]	*J-L Huang*	76·3	Oct-17	15·8	3,036	13·6	2·4	4·2	14·5	0·1	0·2	3·7	1·0	3·7	6·9	1·3	3·8	32·8	7·4	14·7
Thailand	Bangkok[3,4]	*S Chinratanapisit*	86·3	Aug-17	16·1	3,067	14·6	-0·2	-0·3	6·1	-2·9	-4·2	6·8	0·9	1·9	3·0	-1·7	-3·6	24·2	-4·2	-5·1
Region total				Nov-17	16.0	19,925	7·4	-2·5	na	5·6	-3·4	na	2·8	-1·0	na	4·1	-1·3	na	21·4	0·5	na
World total				Aug-17	15·3	45,434	9·9	-1·5	na	9·0	-1·6	na	4·3	-0·5	na	6·4	-0·2	na	24·8	0·5	na

*GAN Phase I

Methodology notes for GAN Phase I centres only: 1 response rate <70%; 2 no date of birth on the questionnaire; 3 <10 schools used when ≥10 schools available; 4 >20% missing age and date of birth.

Chandigarh is not in this Table because it’s ISAAC data is only from Phase I.

Table 3. Model results of estimated change in all asthma related outcomes over 10 years, as absolute percentage difference. Results from mixed model with random intercepts for country and centre, incorporating effect modification, fully adjusted for age group, income group and grouped region (n=416). For full explanation see Methods section of text.

Strata		Outcome					N* in strata
		Current wheeze (95% CI)	Severe asthma symptoms (95% CI)	Exercise wheeze (95% CI)	Night cough (95% CI)	Asthma ever (95% CI)	
Model stratified by age group							
Age 6-7		-0·22 (-1·00, 0·57)	-0·24 (-0·63, 0·15)	0·78 (-0·31, 1·87)	3·21 (1·80, 4·62)	0·56 (-0·13, 1·24)	161
Age 13-14		-0·43 (-1·10, 0·23)	-0·37 (-0·69, -0·04)	0·34 (-0·58, 1·26)	4·25 (3·06, 5·44)	1·25 (0·67, 1·83)	255
Model stratified by age group and income group							
Age 6-7	Low-income	-1·37 (-2·47, -0·27)	-0·84 (-1·37, -0·30)	-0·02 (-1·54, 1·50)	3·33 (1·34, 5·32)	-1·56 (-2·48, -0·65)	31
	Lower-middle-income	1·99 (0·33, 3·66)	1·32 (0·51, 2·12)	3·66 (1·36, 5·96)	5·29 (2·28, 8·29)	0·06 (-1·33, 1·44)	15
	Upper-middle-income	0·50 (-0·82, 1·82)	0·20 (-0·44, 0·84)	1·66 (-0·17, 3·48)	1·41 (-0·98, 3·80)	1·19 (0·09, 2·28)	43
	High-income	-0·22 (-1·24, 0·80)	-0·39 (-0·88, 0·11)	0·25 (-1·16, 1·66)	3·48 (1·63, 5·32)	2·07 (1·22, 2·92)	72
Age 13-14	Low-income	-1·67 (-2·70, -0·64)	-1·03 (-1·53, -0·53)	-0·58 (-2·00, 0·85)	4·31 (2·45, 6·17)	-0·84 (-1·70, 0·02)	47
	Lower-middle-income	1·69 (0·13, 3·25)	1·13 (0·37, 1·88)	3·10 (0·95, 5·25)	6·26 (3·46, 9·07)	0·78 (-0·52, 2·08)	40
	Upper-middle-income	0·19 (-1·06, 1·45)	0·01 (-0·60, 0·62)	1·10 (-0·63, 2·83)	2·38 (0·12, 4·65)	1·91 (0·86, 2·95)	62
	High-income	-0·52 (-1·47, 0·43)	-0·58 (-1·04, -0·12)	-0·31 (-1·62, 1·00)	4·45 (2·73, 6·17)	2·79 (2·00, 3·58)	106
Model stratified by age group and grouped region							
Age 6-7	Africa and Eastern Mediterranean	2·61 (0·76, 4·46)	1·46 (0·57, 2·35)	4·99 (2·41, 7·57)	6·64 (3·28, 9·99)	0·21 (-1·38, 1·79)	10

	America	0·01 (-1·29, 1·31)	0·13 (-0·50, 0·76)	1·23 (-0·56, 3·03)	1·43 (-0·92, 3·77)	0·88 (-0·24, 1·99)	29
	Europe**	1·08 (-0·08, 2·24)	0·43 (-0·13, 0·99)	1·60 (-0·01, 3·21)	4·67 (2·57, 6·78)	2·73 (1·74, 3·73)	64
	South-East Asia and Western Pacific	-1·35 (-2·28, -0·41)	-0·96 (-1·41, -0·51)	-0·33 (-1·64, 0·98)	2·71 (1·01, 4·42)	-0·69 (-1·49, 0·11)	58
Age 13-14	Africa and Eastern Mediterranean	2·09 (0·40, 3·78)	1·15 (0·33, 1·96)	4·15 (1·80, 6·51)	7·41 (4·34, 10·47)	0·78 (-0·68, 2·23)	34
	America	-0·51 (-1·73, 0·71)	-0·19 (-0·77, 0·40)	0·39 (-1·29, 2·07)	2·20 (0·00, 4·40)	1·45 (0·40, 2·50)	50
	Europe**	0·56 (-0·51, 1·63)	0·11 (-0·40, 0·63)	0·76 (-0·73, 2·25)	5·45 (3·50, 7·39)	3·30 (2·38, 4·22)	100
	South-East Asia and Western Pacific	-1·87 (-2·78, -0·96)	-1·28 (-1·72, -0·84)	-1·17 (-2·44, 0·10)	3·49 (1·83, 5·14)	-0·12 (-0·90, 0·66)	71

*N=number of surveys contributing to each stratified analysis

** Malta was in ISAAC's Eastern Mediterranean region for those publications but has been moved to the European region in modelling for this analysis

Authors individual contributions

The following individual contributions were made: conceptualisation IA, KB, C-YC, AES, PE, LG-M, GM, NP, DS; data curation EE, PE, LG-M, EM, VP-F, CR, SR, RS; formal analysis NP, CR, DS; investigation IA; methodology IA, C-YC, PE, LG-M, NP, CR, DS, RS; project administration, IA, EE; PE; resources IA; supervision LG-M, NP, DS, RS; validation PE; visualisation EE, PE, CR; writing – original draft IA, CR; writing – review/editing KB, C-YC, AES, EE, PE, LG-M, EM, KM, VP-F, NP, DS, RS and the Global Asthma Network Phase I Study Group; the latter contributed original data to the analyses. Verification of the underlying data was undertaken by CR, NP, VP-F and DS.

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Data sharing

ISAAC data are already deposited for wider use. The study protocol including a recommended informed consent form and statistical analysis plan are in the public domain. The GAN Phase I data, including de-identified individual participant data, will be made available on the Global Asthma Network website http://www.globalasthmanetwork.org/ within 12 months of all GAN Phase I analyses being published. Access will require a formal request, a written proposal and a signed data access agreement.

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